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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/778,259	02/07/2001	Cristobal Guillermo dos Remedios	13388	4496

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EXAMINER	
CHEU, CHANGHWA J	
ART UNIT	PAPER NUMBER
1641	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/778,259	REMEDIOS ET AL.	
	Examiner	Art Unit	
	JACOB CHEU	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 42-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38, 42-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicant's amendment filed on 1/15/2009 has been received and entered into record and considered.
The following information provided in the amendment affects the instant application:

Claims 1-37, 39-41 are cancelled.
Claim 48 is added.
Currently, claims 38, 42-48 are under examination.

2. The rejections of claims 38, 42-47 are maintained (see below).

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 38, 42-43 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al. (Environ Mutagenesis 1981 Vol. 3, page 545-553) in view of Griffith et al. (US 5354996).

Richardson et al. teach a method of detecting toxic mutagens and carcinogens, including Pb^{+2}, Zn^{+2}, Cd^{+2}, Fe^{+2} and Pt^{+2}(See Abstract; Figure 1 and Table II)(Note, these are metal ions). Richardson et al. teach contacting samples containing the metal ions with nucleic acid molecules intercalated with a fluorescent dye, and detecting the dissociating of the binding between the nucleic acid molecules and said fluorescent dye, wherein said dissociation of the binding is indicative of the presence of the metal ions (See Table II; Figure 1; page 546, last paragraph to page 547, first paragraph for "Acridine Orange Displacement Assay). The assay taught by Richardson et al. can detect these ions in the range of micromolar amounts. supra. Richardson reveal that Pb^{+2}, Zn^{+2}, Cd^{+2}, Fe^{+2} and Pt^{+2}also exist in the environment and associated with cancer (See page 545, Introduction; also the listed epidemiological studies by Sunderman, 1978).

It is noted that the claim recites detecting "ions of metals". Overall, Richardson et al. teach detect several metals of ions as discussed above. In addition, one ordinary skill in the art would have used multiple test tubes and/or array to detect multiple ions *at one time* in *one assay* in saving time and cost (emphasis added).

However, the samples measured by Richardson et al. are from laboratory, not an "environmental sample".

Griffith et al. review of the contamination and pollution of heavy metal ions in the environment, and the need of measuring and monitoring the levels of these heavy metals for public safety and health (Col. 1-25). Particularly, Griffith et al. teach method of measuring the aquatic samples, e.g. waste water (Figure 1 and Figure 2).

Therefore, it would have been prima facie obvious to one ordinary skill in the art at the time the invention was made to have motivated Richardson et al. to apply the method of detection of metals to the monitoring of the environmental aquatic samples as taught by Griffith et al. to monitor heavy metal ions in the aquatic samples. One ordinary skill in the art would have been motivated to do so because public safety and health concern about the pollutions from the ubiquitous heavy metals in our ecosystem.

With respect to the feature of detecting the "toxicity" or "toxic level" recited in claims 47-48, the determined concentration of the metals itself is an indicator of toxicity or toxic level. Note, the results of the recited active steps lead to the knowledge of concentrations or presence of metal ions. The level of the concentration is often used as indicator for toxicity or toxic level in the environmental science field. For instance, the safety concentration set forth by regulatory institute is the threshold for determining toxicity of the environmental samples. It is noted that the level of ion metals as reflected by the degree of color change, can be an arbitrary decision. By observing the magnitude of color change, one artisan would have determined the relative degree of the metal ion existing in the waste water. If the color changes in much more magnitude, one ordinary skill would know the concentration of metal ions in the sample is relatively much higher. This would reflect the potential toxicity of the waste water.

With respect to claim 42, the metal ion detected is a heavy metal, such as cadimum and platinum. (See Richardson et al.; page 545).

With respect to claim 43, the fluorescent dye used by Richardson et al. is the acridine orange. Supra.

4. Claims 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al. in view of Griffith et al., as applied to claim , 42-43 and 47 above, and further in view of Nikiforov et al. (US 5610287).

Richardson and Griffith et al. references have been discussed but no explicit teaching on immobilizing DNA on a solid substrate is mentioned.

Nikiforov et al. teach immobilizing DNA molecules on the substrate of a 96-well microtiter plate to improve analysis in a rapid, convenient and inexpensive manner (Col. 4, line 10-20).

Therefore, it would have been prima facie obvious to one ordinary skill in the art at the time the invention was made to motivated Richardson and Griffith et al. to immobilize DNA molecules on the substrate of a 96-well microtiter as taught by Nikiforov et al. to detect mass samples. One artisan in the field would have been motivated to do so in order to take advantage of time and cost saving.

With respect to claims 44-45, Nikiforov et al. teach the materials for microtiter includes polystyrene (Col. 4, line 33-36).

5. Applicant first argues that the feature of "ions of metals" distinguishes from the reference of Richardson et al. in the following:

"the instant method is distinguished from that of Richardson because Richardson's method does not, among other things, simultaneously detect multiple metals in an environmental sample; and further, Richardson does not teach how to simultaneously detect multiple metals in an environmental sample. As submitted previously, Richardson relates to the measurement of the concentration of metal ion, i.e., a single metal ion at a time, in a laboratory-contrived solution." (See page 5)(emphasis added by Examiner)

" method must be repeated for the detection of each individual metals in a sample. To the contrary, the instant method is a one-step method for simultaneously detecting the presence of different metals in one sample. The result obtained by the present method is achieved by the combined displacement of intercalated fluorescent dye by all of the metals present in the sample." (see page 6)(emphasis added by Examiner).

Applicant's arguments have been considered, but are not persuasive.

As has been discussed in this Office Action, the claim does not recite "one-step" or "simultaneously" for the instant method. In addition, based on the claim language, it merely recites detecting "ions of metals". Richardson's teachings, albeit detecting single metals in one test tube, nevertheless encompasses the scope of the claim because Richardson et al. in fact teach detect multiple "ions of metals" in the assay. Furthermore, one can also interpret the overall assay taught by Richardson et al. is conducted "simultaneously", e.g. performing detection at the same time in *multiple* test tubes containing different ions of metals (emphasis added).

The second point Applicant argued is on the inherent feature of environmental samples. Applicant cited various non-patent literatures in support of the notion that one ordinary skill in the art would not have been motivated to employ the method of Richardson to simultaneously to detect the multiple metals in an environmental samples (see quotation from Ince et al. Arch Environ. Contamin. Toxicol. 1999 Vol. 36, page 365-372; Posthuma et al. Ecotoxicology and Environ. Safety 1997 Vol. 38, page 108-121; Rachlin and Grosso Arch Environ. Contam. Toxicol. 1993 Vol. 24, page 16-20).

Applicant's arguments have been considered, but are not persuasive.

> Metals contamination is well-known and concerns general public. A lot of studies on the effects of metals on cancer carcinogenesis and epidemiology have been published (See the name of the Journal Richardson published "Environmental Mutagenesis" and the Introduction portion of the Richardson's reference). Examiner provided a secondary reference taught by Griffith et al.. Griffith et al. review the contamination and pollution of heavy metal ions in the environment, and the need of measuring and monitoring the levels of these heavy metals for public safety and health (Col. 1-25). Particularly, Griffith et al. teach method of measuring the aquatic environmental samples, e.g. waste water (Figure 1 and Figure 2)(emphasis added). With the method of detecting ions of metals at

hand, one ordinary skill in the art would have been motivated to apply to measure the environmental samples, such as aquatic waste water, to measure the levels of metals in the water to assess the safety or contamination in the water.

Moreover, Applicant argues on the feature of "determining toxicity". Applicant argues that one ordinary skill in the art would not have expected to provide a meaningful measure of toxicity of an environmental sample due to the co-existence of multiple metals in the sample. Applicant also refers to the Declaration submitted previously in support of this notion. Applicant reiterates the similar arguments on additive, synergistic or antagonistic effects on the combination of different metal ions. Applicant argues that such phenomenon affects the overall toxicity (See *8/7/2008* Remarks and Declaration/affidavit). Applicant also addresses the experimental results of mixing metal ions to the binding of fluorescent-DNA submitted in the Declaration (See Table 1 in page 4). In addition, Applicant also provides several literatures in addressing these diverse characteristics of combining metals (See Exhibits D-F and C). Furthermore, Applicant argues that the prevailing view in the art at the time when this invention was made was that the synergistic or antagonistic effects of multiple metal toxicants could only be measured with live whole organism or cell-based assay system. However, in the instant invention, i.e. using "naked" DNA based system, was not contemplated to one ordinary artisan due to lack of cellular machinery (e.g. enzymes, membrane..). Applicant points out the whole organism or cell-based assay was the conventional means for measuring synergistic or antagonistic effects.

Applicant's arguments have been considered, but are not persuasive.

For the feature of "determining toxicity", Examiner has indicated in this Office Action that the level of ion metal itself is an indicator of metal toxicity (see above). The results taught by instant method provide concentration/or presence of the metal ions which can be readily determined by one artisan whether the environmental sample, e.g. waste water, contains abundant or minimal

amount of metal ions based on the observation of the change of the dye color. This would also reflect the potential toxicity on the waste water sample. For instance, the degree of color change is higher, then the presence of the ions of metals is obvious abundant in the samples. This would indicate that the samples contain higher level of ions of metals. To one ordinary skill in the art, higher level of metals is indicative of potential toxicity.

With respect to the notion of "additive, synergistic or antagonistic" effects, such features are not recited in the claim. Examiner acknowledges the experiments submitted in the Declaration (paragraph 10 and Table 1 in page 4). The data show different combinations of metal ions affect the binding to the fluorescence-intercalated DNA. It is noted that the so-called toxicity is the degree of influence on *DNA binding* caused by different combinations of metal ions (emphasis added). Coming both Richardson and Griffith et al. teachings, it would have been within reasonable anticipation to one ordinary skill in the art to have achieved similar results, i.e. synergistic or antagonistic effects. Because all the essential elements recited in the claim have been taught by Richardson and Griffith et al.. Taken together, using the same samples, e.g. same amount of different metal ions, using the same method taught by Richardson, i.e. detection the presence of metals by changing intercalated DNA binding, one ordinary skill would have expected to have the similar results as in Table 1 of the Declaration. As to what the conventional cell-based or whole organism system, Examiner has provided prima facie obviousness in the previous and this Office Action. One ordinary skill in the art would have used the method of Richardson to detect environmental samples for determining the safety or toxicity thereof.

Conclusion

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JACOB CHEU whose telephone number is (571)272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jacob Cheu/
Examiner, Art Unit 1641